TITLE OF THE INVENTION

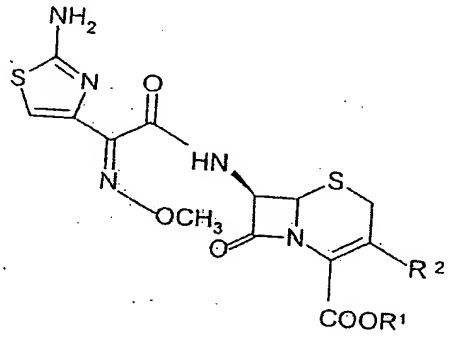
A PROCESS FOR PREPARING CEPHALOSPORINS WITH SALIFIED INTERMEDIATE

ABSTRACT OF THE DISCLOSURE

A process for preparing cephalosporins according to which one 7-ACA is silylated, acylated, desilylated and then salified to give an intermediate which is eventually cyclizated with thiourea.

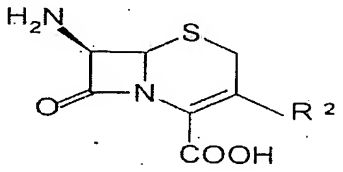
FIELD OF THE INVENTION

Numerous cephalosporins of formula (I)



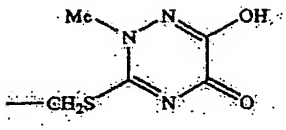
(I)

characterised by the 2-(2-aminothiazol-4-yl)-2-methoxyiminoacetic chain in position 2 of the 7-ACA, and its derivatives of formula (II)

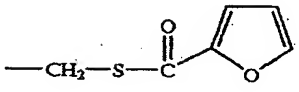


(II)

are known in which R^2 can have various meanings including CH_2OCOCH_3 in the case of 7-ACA, the cefotaxime nucleus or



in the case of 7-ACT, the ceftriaxone nucleus, or



in the case of Furaca, the ceftiofur nucleus.

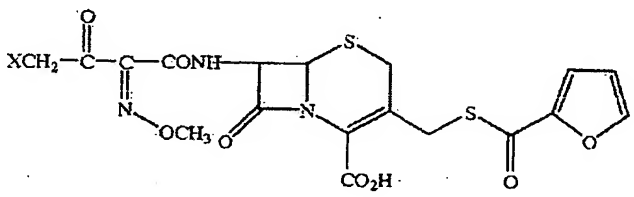
BACKGROUND OF THE INVENTION

Each of these cephalosporins, including those having a different meaning of R^1 and R^2, has been invented and synthesized with its own synthesis method, so that initially there was no common method suitable for producing all cephalosporins having the 2-(2-aminothiazol-4-yl)-2-methoxyiminoacetic chain.

DESCRIPTION OF THE RELATED ART

Recently, in 1996, US 5,583,216 was granted (the filing date of which however was many years previously), generically covering any process usable for inserting the aforesaid chain into 7-ACA and its derivatives. In this manner, any cephalosporin included in the aforesaid group falls within the scope of protection of US 5,583,216 for what concerns the methods used up to the present time for its production, even if that cephalosporin was invented many years prior to the granting of US 5,583,216: however in truth, this patent does not describe any process which can be applied industrially for producing cephalosporins.

To avoid US 5,583,216, considerable research has been carried out, leading inter alia to the granting of US 6,458,949 which claims the intermediate of formula (A)

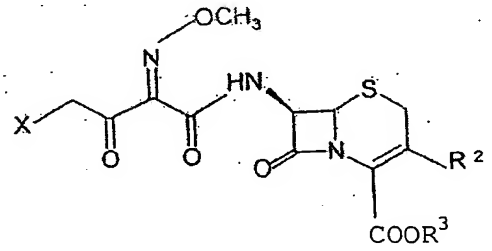


(A)

in which X is Cl or Br, usable for preparing ceftiofur by cyclization with thiourea.

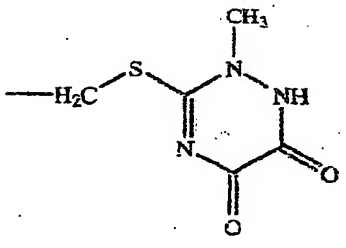
This intermediate is always precipitated in acid form from a solution in methylene chloride at 2-5°C, filtered off, washed with cold water (5°C) and then with methylene chloride. In fact, considering that the precipitate originates from a solution in methylene chloride, according to the usual technique it would have been logical to expect the first wash to have been effected with the same solvent, the water wash being effected only later. This reversal of the wash order and the use of cold water is therefore not random, but points to the fact that the intermediate does not possess great stability and that the water-soluble acid impurities which impregnate the solid just filtered off must be rapidly removed. In addition the intermediate claimed in US 6,458,949, again in acid form, is dried before subsequent cyclization with thiourea, as this reaction is carried out in water-tetrahydrofuran and it is advisable to remove methylene chloride residues. Moreover the maximum obtainable yield is only 75%.

US 6,552,186 claims a compound of formula (IV)

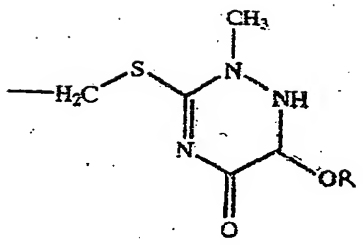


(IV)

in which X is halogen, R^3 is trialkylsilyl and R^2 is



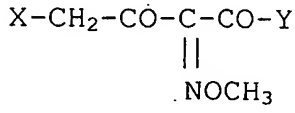
or



This compound is reacted with silylated thiourea to provide a compound of formula (I) in which R^1 and R^2 have the aforesaid meanings and which on subsequent hydrolysis gives the compound having the same formula (I) but in which R^1 is H and R^2 is as aforestated: this compound is ceftriaxone.

US 6,522,186 hence provides a compound of formula (IV) in which R^3 is trialkylsilyl. The corresponding derivative in which R^3 is however H had already been described in US 4,458,072 and obtained as an amorphous product (column 16, line 49) without any indication of the yield, by a laborious process using a precipitating agent such as petroleum ether: this method is certainly unsuitable for industrial use. Again, US 6,552,186 says nothing about yields, as the claimed process comprises direct obtaining of the silylated product of formula (IV) and subsequent reaction with silylated thiourea to give silylated ceftriaxone: the final passage to obtain ceftriaxone disodium salt takes place by the known methods, however overall total process yields are not given.

The recent US 6,458,949 claims a process by which Furaca is silylated and then reacted with a compound of formula (III)



(III)

in which X is Cl or Br and Y is Cl, or

$O-CH=N^{+}(CH_3)_2Cl^{-}$

to isolate an aforestated compound of formula (A), in which X is Cl or Br and the carboxyl is free, non-salified and non-esterified.

When reacted with thiourea in a partly aqueous solvent, this intermediate produces ceftiofur.

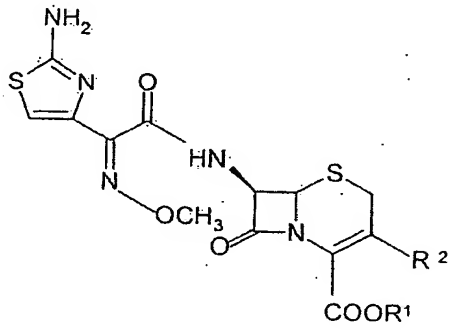
Compounds of formula (III) have been known for some time: for example, GB 2,012,276 describes in example 5 the preparation of a compound of formula (III) in which the methoxyimino group is substituted by the ethoxyimino group, X is Br and Y is Cl, by reacting the corresponding acid having the same formula (III) but in which X is Br and Y is OH, with PCl_5 in a dichloromethane solution. According to example 13 of the patent, 7-(4-chloro-3-oxo-2-methoxyiminobutyryl-amino)cephalosporanic acid is subsequently reacted with thiourea to give a sodium salt of 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido)cephalosporanic acid, this being cefotaxime,

EP 30294 (page 4, lines 36-37 and 40-45), US 6,384,215 (column 3, lines 19-20) and US 6,458,949 (column 4, line 1; column 5, line 2 and lines 47-48) also describe the preparation of compounds of formula similar to formula (III).

It is therefore apparent that compounds of formula (III) in activated form, able to react with a compound of formula (II) silylated at the carboxyl, can be prepared for example as chlorides by reaction with PCl_5 or other chlorinating agents, such as $POCl_3$ and DMF, in dichloromethane.

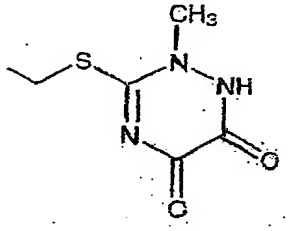
SUMMARY OF THE INVENTION

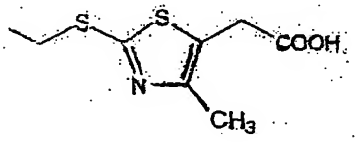
The object of the present invention is to provide a process of high efficiency in terms of final product yield and purity, for producing ceftiofur, cefotaxime, ceftriaxone, and cephalosporins generally, characterised by the same general formula (I)

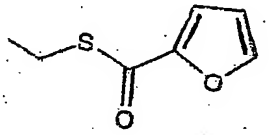


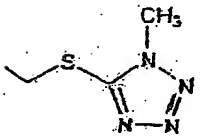
(I)

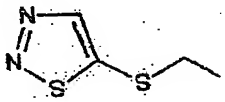
in which R^1 is H or Na and R^2 is chosen from the group consisting of H, CH_3, CH_2OCH_3, CH_2OCOCH_3, $CH{=}CH_2$,

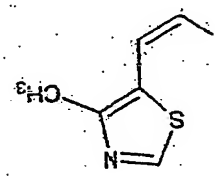




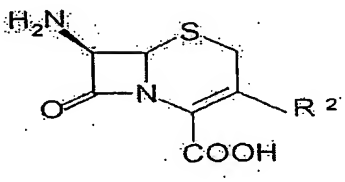






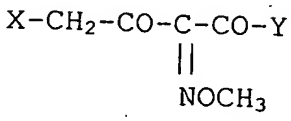


According to this process, a compound of formula (II)



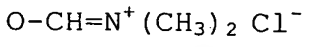
(II)

in which R^2 has the aforestated meanings is silylated at the carboxyl to give the corresponding trialkylsilyl-ester which is reacted with a compound of formula (III)

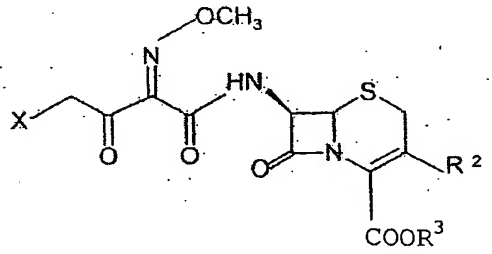


(III)

in which X is Cl or Br and Y is Cl, or

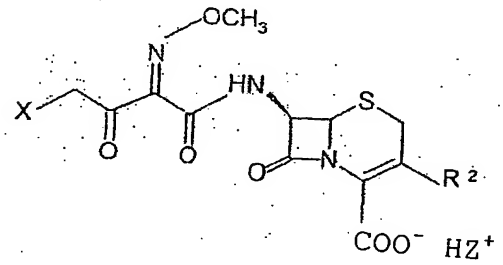


to give a cephalosporin of formula (IV)



(IV)

in which X and R^2 have the aforestated meanings, and R^3 is trialkylsilyl, which is hydrolyzed at pH 7÷7.5 and then treated in a partly aqueous solution with benzathine or a salt thereof, to obtain crystallization of a new cephalosporin of formula (V)



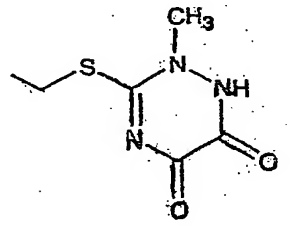
(V)

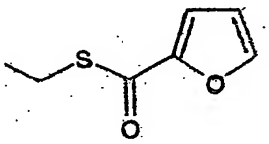
where Z is benzathine, in which the carboxyl is salified by the benzathine, this salt being filtered off, washed with water and reacted in a partly aqueous solvent with thiourea, to lead to the formation of the 2-(2-aminothiazol-4-yl)-2-methoxyiminoacetic chain and give a solution of the compound of general formula (I)

in which R^2 has the aforestated meanings and R^1 is H, the compound of formula (I) being crystallized from this solution in the form of the sodium salt, of the salt of a pharmaceutically acceptable inorganic acid or of an internal salt.

Simultaneously with the formation of the 2-(2-aminothiazol-4-yl)-2-methoxyyminoacetic chain there may be the precipitation of benzathine hydrochloride which is filtered off and removed to leave a very pure solution of the compound of general formula (I).

In particular, it has been surprisingly found possible to quantitatively isolate in aqueous solution a cephalosporin of formula (V), in which R^2 is CH_2OCOCH_3, or





without any interaction with the halogen atom X present in the compounds of formula (V).

This precipitation in aqueous solution automatically eliminates all the acid impurities originating from the preparation of the aforesaid compounds of formula (V), then by simply washing with water a high purity moist product is obtained ready for subsequent reaction with thiourea in a partly aqueous environment.

A further considerable advantage of the present invention derives from the fact that the cyclization reaction with thiourea, leading to the formation of HCl, finds in benzathine a base able to subtract it from the solution as the hydrochloride insoluble under reaction conditions. In this manner a solution is

obtained containing only cephalosporin in acid form of such purity as to enable it to be very easily crystallized as the sodium salt, by adding a sodium salt such as sodium acetate or sodium 2-ethyl-hexanoate.

This succession of operations will be more apparent from the non-limiting examples which follow.

However, the same operative scheme can evidently be applied for the production of cephalosporins other than ceftiofur, cefotaxime and ceftriaxone, having nuclei different from the aforespecified three, but having the same 2-(2-aminothiazol-4-yl)-2-methoxyiminoacetic side chain in position 7.

DETAILED DESCRIPTION OF THE INVENTION

EXAMPLE 1 - Preparation of Sodium Ceftiofur

Two separate solutions are prepared.

Solution A

40 g of FURACA (MW 340.38 - 0.118 moles) and 336 ml of tetrahydrofuran are fed into a dry 1 litre flask under a nitrogen flow in the absence of direct light. The mixture is agitated for 15 minutes until homogenization, while cooling in the meantime to +10°C.

While maintaining the temperature at +10°C÷+12°C, 1.486 ml of trimethylchlorosilane (MW 108.64 - d=0.859 - 0.1 eq) are quickly added. The mixture is agitated for 5 min at +10°C÷+12°C, and 45.43 g of N,O-bis-trimethylsilyl-acetamide (MW 203.43 - d=0.832 - 1.9 eq) are added over 5÷10 minutes.

The temperature is raised to +20°C and the mixture agitated for 1h35min at 22°C÷23°C until a solution is obtained. It is cooled to -35°C÷-40°C.

Solution B

210 ml of ethyl acetate and 13.02 ml of N,N-dimethylformamide (MW 73.094 - 0.169 moles - d=0.95 -

12.37 g) are fed into a dry 1 litre flask under a nitrogen flow.

15.49 ml of phosphorus oxychloride ($POCl_3$) (0.167 moles - MW 153.33 - d=1.675 - 25.95 g) are added at +25°C, allowing the temperature to rise to +36°C.

The mixture is cooled to 0°C and 27.62 g of 4-chloro-3-oxo-2-methoxyimino-butyric acid, commonly known as COMBA (MW 179.56 - 0.154 moles) are added without exceeding +5°C. The mixture is agitated for 1 hour at + 5°C.

Solution B is added dropwise to solution A over 15 minutes maintaining the temperature at -35°C÷-40°C. The reaction terminates within 2 hours at -35°C÷-40°C.

On termination of the reaction the mixture is poured into 500 ml of water at 0°C, maintaining the pH at 7.0÷7.5 with triethylamine, while maintaining the temperature at 0°C.

200 ml of ethyl acetate are added and the phases are separated at 0°C÷+5°C. Extraction is again effected at pH 7.0÷7.5 with 350 ml of water.

The aqueous phase is decolorized at 0°C÷+5°C for 30 minutes with 4 g of carbon and 0.4 g of EDTA. It is filtered and washed with 150 ml of water.

The pH is adjusted to 7.0÷7.5 with triethylamine at 0°C÷+5°C using a total of 110 ml thereof.

A mixture of 43.25 g of benzathine diacetate (0.120 moles) dissolved in 350 ml of water is added dropwise, then washing with 50 ml of water.

It is left to precipitate cold at 0°C÷+5°C for about 90 minutes.

The precipitate is filtered off and washed with 500 ml of water divided into two portions.
It is left to drip well.

The condensation product of 7-FURACA with activated COMBA, precipitated moist as benzathine salt, is used as such in the next passage.

A sample is dried for analysis.

The moist benzathine salt obtained as described is suspended in 740 ml of tetrahydrofuran at +20°C÷+25°C.

It is cooled to 0°C÷+5°C and 19 ml of triethylamine are added, maintaining this temperature.

12 g of thiourea are added at 0°C÷+5°C and the mixture agitated for 18 hours.

It is cooled to 0°C÷+5°C and, while maintaining this temperature, 600 ml of ethyl acetate are added plus about 20 ml of concentrated hydrochloric acid to pH 3. The precipitated benzathine hydrochloride is filtered off and the filter washed with a mixture of 60 ml of tetrahydrofuran + 60 ml of ethyl acetate.

400 ml of water are added to the filtrate solution.

The temperature is raised to +10°C÷+15°C and the pH adjusted to 8.0÷ 8.5 with 15 ml of triethylamine.

The phases are separated.

The impoverished organic phase is re-extracted with a further 400 ml of water at pH 8.0÷8.5, the aqueous phases are pooled and washed with 300 ml of ethyl acetate. 400 ml of tetrahydrofuran are added to the aqueous phase.

The mixture is cooled to 0°C÷+5°C and the pH adjusted to 3 with 1N hydrochloric acid. 300 g of sodium chloride are added and the mixture agitated until a solution forms, while raising the temperature to +15°C÷+20°C.

The phases are separated, the overlying organic phase being rich in product. Carbon is added to the organic phase at +15°C÷+20°C and the mixture agitated

for 20 minutes. The mixture is filtered and washed with 100 ml of tetrahydrofuran.

A homogeneous mixture of 28.88 g of sodium 2-ethylhexanoate and 100 ml of tetrahydrofuran is added dropwise to the decolorized organic phase over 20 minutes.

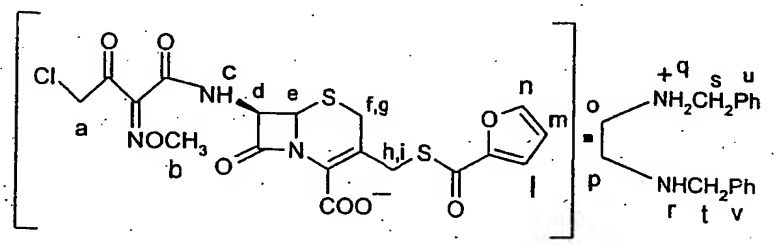
The mixture is agitated for 15 minutes at +15°C÷+20°C.

The solution obtained is added dropwise over 30 minutes to 1000 ml of agitated tetrahydrofuran at +20°C.

The mixture is agitated for 2 hours at +20°C, filtered and washed with 320 ml of acetone.

The product is dried at +30°C÷+32°C to obtain 51.3 g of sodium ceftiofur.

The dried sample of benzathine salt has the following general formula (V), and more specifically has the general formula



which provides the following spectra:

^{1}HNMR in DMSO-d_6 300 Mhz; Hc = 9.40 ppm 1H; Hn = 8.04 ppm 1H; Hu-Hv = 7.32-7.46 ppm 10H; Hl = 7.39 ppm 1H; Hm = 6.77 ppm 1H; Hd = 5.68 ppm 1H; He = 5.06 ppm 1H; Hq-Hr = 4.84 ppm 3H; Hb = 3.95 ppm 3H; Hh-Hi = 4.22-3.99 ppm 2H; Hf-Hg = 3.65-3.26 ppm 2H; Hs-Ht = 4.03 ppm 4H; Ho-Hp = 2.95 ppm 4H; Ha = 3.97 ppm 2H.

FT-IR (cm^{-1}); 1777.6-1717.1-1650.7-1565.8

EXAMPLE 2 -Preparation of ceftriaxone disodium salt

Two separate solutions are prepared.

SOLUTION A

15.57 g of 7-ACT (MW 371.39 - 0.042 mol) and 155 ml of methylene chloride are fed into a dry 1 litre flask under a nitrogen flow in the absence of direct light. The mixture is cooled to +10°C and 34.11 g of N,O-bis-trimethylsilyl-acetamide are added, a slight amount of heat being produced. The mixture is agitated at +20÷22°C and after 45 minutes a complete solution is obtained. The mixture is cooled to -40°C.

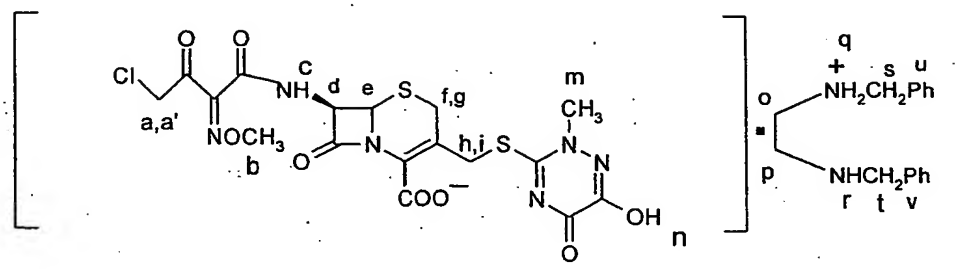
SOLUTION B

80 ml of ethyl acetate and 4.69 ml of N,N-dimethylformamide (MW 73.09, d=0.95) are fed into a dry 1 litre flask under a nitrogen flow at +25°C. 5.58 ml of phosphorus oxychloride (MW 153.33, d=1.675, 9.34 g) are added allowing the temperature to rise to 36°C (if this temperature is not attained within 20÷25 minutes, heating is required). The mixture is cooled to 0°C then 9.94 g of 4-chloro-3-oxo-2-methoxyimino-butyric acid, commonly known as COMBA (MW 179.56) are added. The mixture is agitated at +5°C for 1 hour. Solution B is added dropwise to solution A over 15÷20 minutes maintaining the temperature at -35°÷-40°C and washing the flask with 15 ml ethyl acetate. The mixture is agitated for 10 minutes at -35°÷-40°C and the reaction goes to completion. The reaction mixture is poured into a mixture of 50 ml water, 320 ml isopropanol and 270 ml of a saturated aqueous solution of sodium bicarbonate pre-cooled to 0°÷-5°C without exceeding +5°C. It is agitated for 2 hours at 0°÷+5°C maintaining the pH at 2.5 (consuming about 27 ml of 17% hydrochloric acid), the pH being checked for about 90 minutes, during which

any necessary correction is done with solid sodium bicarbonate. The phases are separated and the underlying aqueous phase is retained. The rich organic phase is washed with 25 ml water, then with a solution of 22 g NaCl in 80 ml water. The aqueous phases are retained each time and pooled, then re-extracted with 40 ml methylene chloride. The organic phases are pooled and the spent aqueous phase is discarded. The former is decolorized under agitation for 15 minutes with 1.5 g carbon, filtered and the filter is washed with 30 ml of methylene chloride. 150 ml of water are added to the decolorized organic phase at 0°÷+5°C followed by, still at 0°÷+5°C, a solution of 11.21 g anhydrous sodium acetate in 100 ml water pre-cooled to 0°÷+5°C. After 30 minutes the phases are separated allowing the temperature to rise to about +20°C. The poor organic phase is re-extracted with 100 ml of water, facilitating separation with 50 ml of methylene chloride. The aqueous phases are pooled and decolorized at +20°C for 30 minutes with 1.5 g of carbon, 0.150 g of EDTA and 0.200 g of celite. The mixture is filtered and the filter is washed with 100 ml water.

A solution of 15.14 g of benzathine diacetate in 160 ml demineralised water is added over 15 minutes to the decolorized solution at 15°÷20°C. The mixture is agitated for 30 minutes at 15°÷20°C, cooled to 0°÷+5°C and agitated for 1 hour. It is filtered and washed 3 times with 50 ml of water. It is thoroughly squeezed under a nitrogen flow to obtain 28.52 g of the benzathine salt of the condensation product of 7-ACT with COMBA. A sample is dried for analysis.

The dried sample of benzathine salt has the general formula (V), and more specifically has the formula



which provides the following spectra:

^{1}HNMR in DMSO-d_6 300 MHz: Hc = 9.36 ppm 1H; Hu-Hv = 7.30-7.42 ppm 10H; Hd = 5.65 ppm 1H; He = 5.03 ppm 1H; Ha-Ha' = 4.84 ppm 3H; Hb = 4.03 ppm 3H; Hq-Hr = 3.91 ppm 3H; Hh-Hi = 4.35-4.12 ppm 2H; Hm=3.50 ppm 3H; Hf-Hg = 3.62-3.39 ppm 2H; Hs-Ht = 3.53 ppm 4H; Ho-Hp = 2.89 ppm 4H.

FT-IR (cm^{-1}): 1775.1-1715.7-1666.6-1594.1

The benzathine salt obtained is suspended in 200 ml water and 142 g of the sulfonic resin Resindion UBK 530 in sodium form and 6.38 g of thiourea are added at 20°÷25°C. The mixture is agitated for 4 hours at 20°÷25°C, filtered and washed 8 times with 50 ml of water each time and then decolorized for 20 minutes at 15°÷20°C with 1.5 g of carbon, 0.150 g of EDTA and 0.200 g of celite. The carbon is filtered off and the filter is washed 4 times with 50 ml water. The pH is adjusted to about 4.2 with 7 ml of 17% hydrochloric acid at 15°/20°C, until precipitation begins. It is agitated for 30 minutes, and adjusted to pH 3 over 40

minutes at 15°÷20°C with about 13 ml of 17% hydrochloric acid.

It is filtered off, washed twice with 50 ml water and thoroughly squeezed to obtain 45 g of crude ceftriaxone acid (K.F. = about 60%).

79.5 ml of acetone, 20 ml of water, 80 g of carboxylic resin RELITE CNS (activated in sodium form) are fed into a flask. The mixture is cooled to +10°C and 45 g of well-sifted crude ceftriaxone acid obtained above are added, then agitated at +10°C for 4 hours until the dissolved ceftriaxone content remains constant. The resin is filtered off, washed with a mixture of 10 ml water + 8 ml acetone and then with a mixture of 6 ml water and 19 ml acetone, maintaining these washes separate from the initial filtrate and at +10°C. The initial filtrate is maintained under agitation with 1.33 g carbon, 0.07 g EDTA and 0.13 g celite, for 45 minutes at +10°C. This is filtered off and washed with the mixture of the two washes kept separate from the initial filtrate, the decolorized solution being diluted with 79.5 ml acetone added dropwise over 10 minutes at +10°C. It is seeded with disodium ceftriaxone and agitated for 90 minutes at +10°C. 291.5 ml of acetone are then added dropwise over 3 hours at +10°C. The product is filtered off and washed with 106 ml portions of acetone, thoroughly squeezed under a nitrogen flow then dried at ambient temperature until constant weight, to obtain 22.5 g disodium ceftriaxone.

EXAMPLE 3 - Preparation of cefotaxime sodium salt

Two separate solutions are firstly prepared.

SOLUTION A

64 g of 7-ACA (MW 272.28 - 0.235 mol) and 400 ml of tetrahydrofuran are fed into a dry 1 litre flask

under a nitrogen flow and in the absence of direct light. The mixture is agitated for 15 minutes until homogenized while cooling to +15°C.

191.34 g of N,O-bis-trimethylsilyl-acetamide (MW 203.43, d=0.832, 0.941 mol) are quickly added, maintaining the temperature at 20°÷25°C. The temperature is maintained at 20°÷25°C while the mixture is agitated for 15 minutes at +20°÷+25°C until dissolved, then cooled to -35°C÷-40°C.

SOLUTION B

420 ml of ethyl acetate and 26.04 ml of N,N-dimethylformamide (MW 73.09, d=0.95, 0.338 mol, 24.74 g) are fed into a dry 1 litre flask under a nitrogen flow at +25°C. 30.98 ml of phosphorus oxychloride (MW 153.33, d=1.675, 51.9 g) are added allowing the temperature to rise to 36°C (if this temperature is not attained in 20÷25 minutes, heating is required).
The mixture is cooled to 0°C then, without exceeding +5°C, 55.24 g of 4-chloro-3-oxo-2-methoxyimino-butyric acid, commonly known as COMBA (MW 179.56 - 0.308 mol) are added. The mixture is agitated at +5°C for 1 hour.
Solution B is added dropwise into solution A over 15÷20 minutes while maintaining the temperature at -35°÷-40°C.

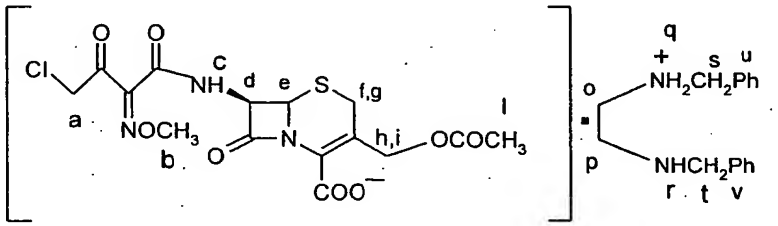
The reaction terminates within about 45 minutes at -35°÷-40°C. At the end of the reaction 600 ml of water at 0°C are poured in, adjusting the pH to 7÷7.5 with triethylamine and maintaining the temperature at 0°÷+5°C.

The organic phase is extracted again with 450 ml of water at 0°÷+5°C, maintaining the pH at 7÷7.5.

The aqueous phases are pooled and a solution of 85.05 g of benzathine diacetate in 800 ml of water is added dropwise over 60 minutes, maintaining the temperature at 0°÷+5°C. It is agitated for 1 hour at 0°÷+5°C, the product is filtered off then washed twice with 250 ml water and thoroughly squeezed. 152 g of moist condensation product of 7-ACA with COMBA as the benzathine salt are obtained.

A sample is dried for analysis.

The dried sample of benzathine salt has the general formula (V) and more specifically has the formula



which provides the following spectra:

^{1}HNMR in DMSO-d_6 300 MHz: Hc = 9.42 ppm 1H; Hu-Hv = 7.36-7.46 ppm 10H; Hd = 5.73 ppm 1H; He = 5.03 ppm 1H; Hq-Hr = 4.85 ppm 3H; Hb = 3.95 ppm 3H; Hh-Hi = 4.11-4.03 ppm 2H;

Hf-Hg = 3.55-3.36 ppm 2H; Hs-Ht = 3.99 ppm 4H; Ho-Hp = 3.05 ppm 4H; Ha = 2.03 ppm 2H.

FT-IR (cm^{-1}): 1766.3-1719.5-1660.0-1555.8

The moist product obtained is suspended in a mixture of 320 ml of tetrahydrofuran and 80 ml of water, cooled to 0°÷-5°C and 22 ml of triethylamine are added to pH 7.5. 24.84 g of thiourea are added and left to react for 4 hours at +20°÷+25°C until

conversion of the aforestated condensation product to cefotaxime is complete.

On termination of the reaction 1.6 g of sodium hydrosulfite, 0.4 g of EDTA, 0.8 g of celite and 4 g of carbon are added and the mixture is agitated for 20 minutes then filtered, washing the product with 80 ml of tetrahydrofuran. The tetrahydrofuran is evaporated under reduced pressure until an oily residue forms. 368 ml of water are added dropwise to the oil obtained under agitation.

233.6 g of 99% formic acid are dropped over a period of 5÷10 minutes at +15°÷+20°C into the suspension obtained.

It is cooled to 0°÷+5°C and agitated for 3 hours, filtered and the product washed with 96 ml of water pre-cooled to 0°÷+5°C. The product is suspended in 384 ml of ethanol at 45÷50°C and agitated for 1 hour. It is filtered off while hot then washed with 192 ml of ethyl acetate.

After drying, 36 g of cefotaxime ethanol solvate with a concentration of 85% is obtained, serving as intermediate.

227.5 ml of methanol, 28.2 ml of water and 32.8 g of sodium 2-ethylhexanoate are fed into a flask under a nitrogen flow. The mixture is agitated at ambient temperature until completely dissolved and cooled to 0°÷+5°C. The intermediate cefotaxime acid ethanol solvate (87.5 g) is added and complete dissolution is achieved at 0°÷+5°C. The temperature is maintained and 350 ml of ethyl acetate are added over 1 hour. The solution is seeded with cefotaxime sodium salt and agitated for 1 hour at 0°÷+5°C. A further 263 ml of ethyl acetate are added over 40 minutes, then a further

875 ml of ethyl acetate over 1 hour at 0°÷5°C. The mixture is agitated for 30 minutes at the same temperature, filtered and the product washed with 88 ml ethyl acetate and dried at 30°C under reduced pressure. Yield: 80.5 g of cefotaxime sodium salt.

EXAMPLE 4 - PREPARATION OF CEFTIOFUR HYDROCHLORIDE

Two separate solutions are prepared.

SOLUTION A

20 g of Furaca (MW 340.38 - 58.76 mmol) and 168 ml of tetrahydrofuran are fed into a dry 1 litre flask under a nitrogen flow and in the absence of direct light. The mixture is agitated for 15 minutes until homogenized while cooling to +10°C. At +10°÷+12°C 0.743 ml of trimethylchlorosilane (MW 108.64 - d=0.859) are quickly added. The mixture is agitated for 5 minutes at +10°÷+12°C and then 22.72 g BSA (MW=203.43) are added over 5÷10 minutes.

The temperature is raised to +20°C and the mixture is agitated for 95 minutes at +22°÷+23°C until completely dissolved. It is then cooled to -35°÷-40°C.

SOLUTION B

105 ml of ethyl acetate and 6.51 ml of dimethylformamide (PM 73.09, d=0.95) are fed into a dry 1 litre flask under a nitrogen flow. At +25°C 7.75 ml of $POCl_3$ (MW 153.33, d=1.675) are added, allowing the temperature to rise to +36°C over 20÷25 minutes, if necessary heating it slightly. The mixture is cooled to 0°C and then 13.81 g of 4-chloro-3-oxo-2-methoxyimino-butyric acid, commonly known as COMBA (MW 179.56) are added taking care not to exceed +5°C. Agitation is maintained at +5°C for 60 minutes.

Solution B is added dropwise into solution A over 15 minutes, maintaining the temperature at -35°÷-40°C. It is left to react for 2 hours at the same temperature.

On termination of the reaction the reaction mixture is poured into 100 ml of iced water, correcting the pH to 3.0 with about 20 ml of triethylamine and maintaining the temperature at 0°÷+5°C. The temperature is raised to +15°÷+20°C and the phases are separated. The aqueous phase is again extracted with 100 ml of ethyl acetate, the organic phases are pooled and decolorized with 2 g of carbon maintaining agitation for 20 minutes at 15°÷20°C. The latter is filtered off, the filter is washed with 25 ml of tetrahydrofuran and then with 25 ml of ethyl acetate.

The solution is cooled to 0°÷+5°C and 200 ml water at 0°÷+5°C are added. At the same temperature the pH is corrected to 8 with about 13 ml of triethylamine.

The phases are separated and extracted twice more with 100 ml water maintaining the pH at 8 with 3 ml of triethylamine. The aqueous phases are pooled and a solution of benzathine diacetate (27.75 g, MW 360.4) in 262.5 ml water is added dropwise over 30 minutes, at 0°÷+5°C, then the remaining benzathine solution left in the dropping funnel is recovered, washing it with water (37.5 ml). Agitation is maintained for 2 hours at 0°÷+5°C, then the product is filtered off and allowed to well drain, then finally washed 4 times, each time with 50 ml of water. 112 g of intermediary product as moist benzathine salt are obtained, with a K.F. of about 60%.

The moist product with the aforestated K.F., is suspended in tetrahydrofuran (250 ml) at +20°÷25°C. 200 g of UBK530 resin in sodium form and 5.86 g of thiourea are added in the stated order to the suspension obtained, the pH then being corrected to 8.0÷8.5 with triethylamine (2.5 ml).

Agitation is maintained for 3 hours at 20°÷25°C, then further triethylamine (3.5 ml) is added to correct the pH to 7.5÷8.0. After further agitation for 20 hours at 20°÷25°C, a final reaction pH of 2.5÷3.0 is achieved. The resin is filtered off and washed with 2 x 50 ml portions of tetrahydrofuran, then twice with a mixture of 25 ml tetrahydrofuran + 25 ml of ethyl acetate and finally with 25 ml of water.

Triethylamine (7.5 ml) is added to achieve pH 8.0÷8.5 and then ethyl acetate (200 ml). The phases are separated and the aqueous phase is decolorized with 2 g of carbon, adding 0.2 g of EDTA and 0.2 g of celite and agitating for 20 minutes.

The organic phase is re-extracted with 100 ml of water, which is used to wash the filter following decolorization, whereas the organic phase is finally removed.

125 ml of tetrahydrofuran are added to the decolorized aqueous phase, cooled to 0°÷+5°C and the pH corrected to 3 with about 60 ml of 1N HCl. 50 g of sodium chloride are then added at the same temperature, the mixture is heated to +15°÷+20°C and the phases are separated.

Water (250 ml) is added to the organic phase and the pH is adjusted to 8.0÷8.5 with triethylamine (about 12.5 ml), then ethyl acetate (250 ml) is added.

The phases are again separated, the organic phase is re-extracted with water (150 ml) at pH 8.0÷8.5 The aqueous phases are pooled, washed 3 times with ethyl acetate (200 ml each time), the aqueous phase is decolorized with 2g of carbon + 0.2 g EDTA + 0.2 g celite.

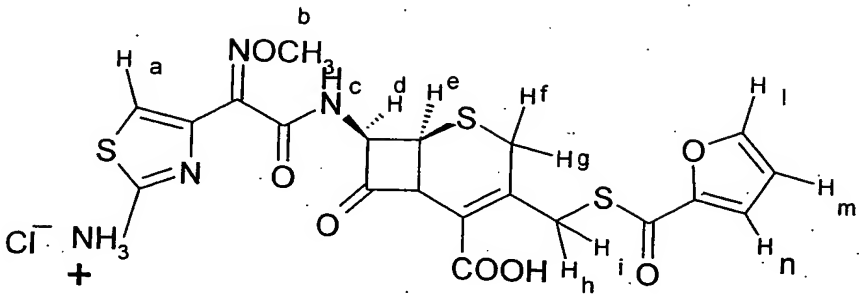
This is filtered off and washed with water (100 ml), the solution is cooled to 0°÷+5°C and the pH is adjusted to 3 with about 48 ml of 1N HCl. It is agitated while cold for 1 hour, the product is filtered off and washed twice with 100 ml water. It is left to drip well under nitrogen, to obtain 114 g of moist product.

The moist solid is suspended in tetrahydrofuran (125 ml) and agitated at 20°C until dissolution is virtually complete, after about 30 minutes, then a saturated aqueous solution (50 ml) of sodium chloride is added and further agitated until complete homogenisation of the mixture.

The phases are separated. The organic phase is decolorized with 2g carbon at 20°C, filtered and washed with 50 ml tetrahydrofuran. It is cooled to 0°÷+5°C, the pH is corrected to 0.5 with concentrated HCl (about 5.5 ml) and maintained under agitation for 10 minutes at 0°÷+5°C.

The acid solution is added dropwise over 45 minutes to 1500 ml acetone while agitated at 20°C. Agitation is continued for a further 60 minutes at 20°C, then the mixture is cooled to 0°/+5°C and again agitated for a further 60 minutes. The product is filtered off and washed with 150 ml acetone to obtain 29 g of moist product.

It is dried at 20°C to obtain 20.5 g of ceftiofur hydrochloride.



CEFTIOFUR HYDROCHLORIDE ^{1}HNMR

9.79ppm doublet Jcd=8.1Hz Hc
8.06ppm Hn ddd system abc
7.44ppm Hm ddd system abc
6.91ppm Hl ddd system abc
6.76 ppm singlet Ha
5.76 ppm Hd dd Jcd=8.1, Jde=5.16Hz
5.16 ppm He doublet Jde=5.16Hz
4.27 ppm, 3.93 ppm Hh, Hi system ab two doublets Jhi=13.2Hz
3.74ppm, 3.38ppm Hf, Hg two doublets system ab Jfg=17.6Hz
3.92ppm Hb singlet

CEFTIOFUR HYDROCHLORIDE FT-IR

amide NH stretching 3273 cm^{-1}
lactam C=O 1766.3 cm^{-1}
thioester C=O 1709.0 cm^{-1}
carboxyl C=O 1659.4 cm^{-1}
amide C=O 1629.4cm^{-1}